Application No. 09/920,435
Filed: August 1, 2001
TC Art Unit: 1639
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REMARKS

Claims 1-14, 21 and 22 are pending in the present application. The Examiner has rejected claims 1-14, 21 and 22 under 35 U.S.C. § 103 as obvious based on a combination of journal articles to Kaur et al. and van Breemen et al. Applicants respectfully request reconsideration and withdrawal of the rejections by the Examiner based on the remarks presented herein.

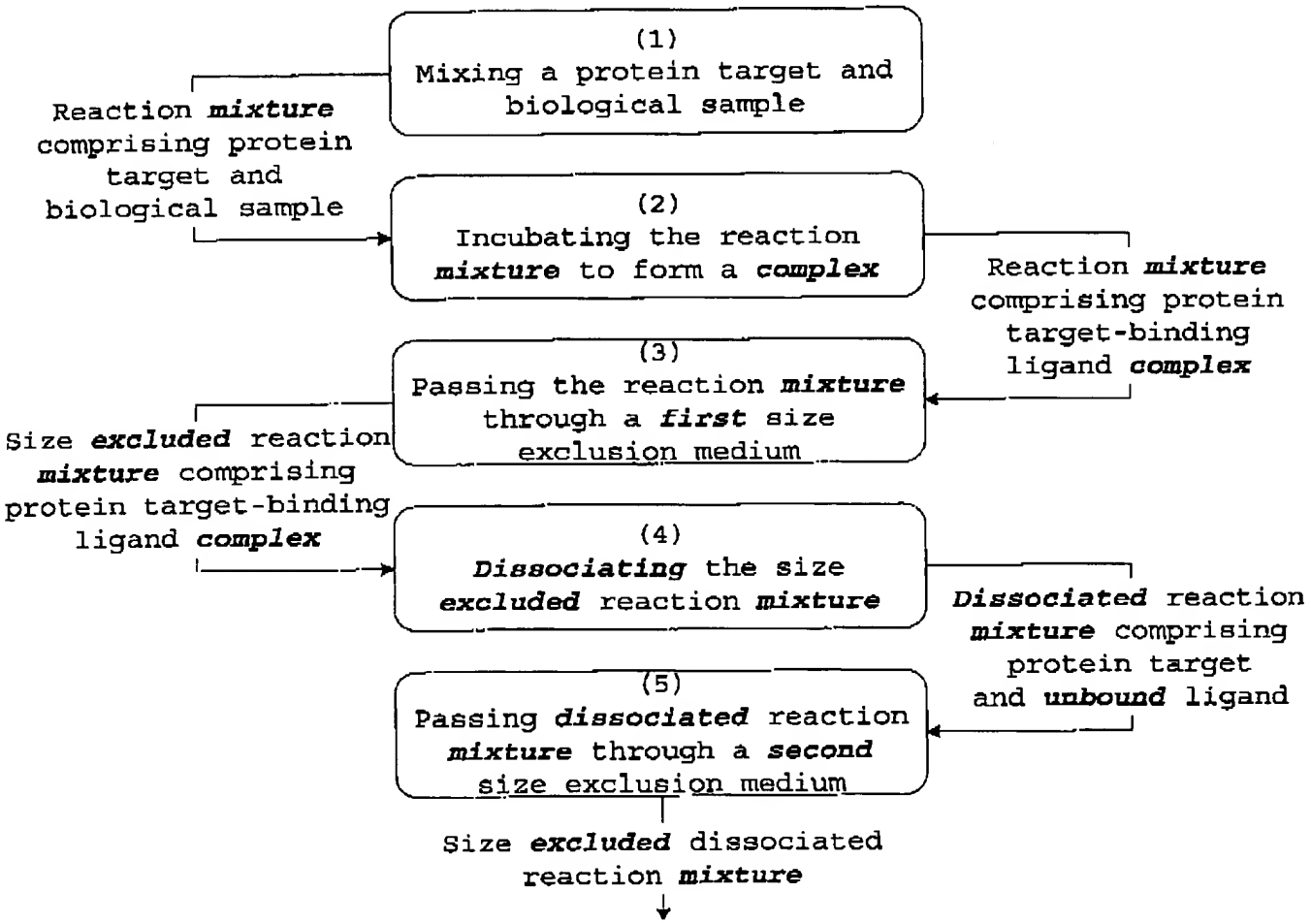
Outstanding Claim Rejections 35 U.S.C. § 103

The Examiner has rejected claims 1-14, 21 and 22 as obvious based on a combination of journal articles to Kaur et al. and van Breemen et al. The Examiner has asserted that Kaur et al. teach each of the limitations of the claimed method without reference to a second size exclusion medium as required by the pending claims. The Examiner has contended that van Breemen et al. disclose pulsed ultrafiltration-mass spectrometry that can be used as a substitute for the mass spectrometry of Kaur et al. such that a combination of the references provides a second size exclusion medium. Applicants respectfully disagree with the contentions of the Examiner and the characterizations of the teachings in Kaur et al. and van Breemen et al. Applicants particularly submit that van Breemen et al. do not teach pulsed ultrafiltration-mass spectrometry that acts as a second size exclusion medium.

Applicants indicate that van Breemen et al. suggest pulsed ultrafiltration-mass spectrometry in which ultrafiltration of a ligand-receptor ***complex*** is performed. The ultrafiltration taught by van Breemen et al. also occurs ***prior*** to any ***dissociation*** of the ligand-receptor ***complex***. A teaching that discloses performing ultrafiltration of a ***complex*** prior to its ***dissociation*** cannot be

applied to render the second size exclusion medium limitation of the claimed method obvious. Applicants also contend that such a teaching cannot be properly combined with Kaur et al. to establish a prima facie basis for the obviousness of the pending claims.

Applicants maintain that the claimed method requires passing a reaction mixture or ***complex*** through a ***first*** size exclusion medium and subjecting the size excluded reaction mixture to ***dissociation*** prior to passing the dissociated mixture through a ***second*** size exclusion medium. A diagram of the claimed method underscores the breadth of the pending claims.



The diagram clearly indicates a method in which a protein target-binding ligand ***complex*** is introduced to (3) a ***first*** size exclusion medium. The ***first*** size exclusion medium operates to ***exclude*** material that does not comprise the ***complex***. The ***complex*** is thereafter (4) ***dissociated*** to comprise the protein target and ***unbound*** ligand. The ***dissociated*** protein target and ***unbound*** ligand are subjected to (5) a ***second*** size exclusion medium that ***excludes*** molecules that are larger than a preset value. The diagram also identifies the yield or product from performing each of the stages and providing such to a latter stage.

In comparison, the journal article to van Breemen et al. teaches separating a ligand-receptor ***complex*** from unbound material by ultrafiltration and ***dissociating*** the isolated ***complex*** after the separation. The ***dissociated*** complex is then passed onto a mass spectrometer. The article does not mention an ***exclusion*** or separation of the ***dissociated*** mixture comprising the receptor and unbound ligand. The journal article also does not disclose ***isolating*** molecules in the ***dissociated*** receptor and ***unbound*** ligand mixture prior to analysis via a mass spectrometer or related method. Thus, an individual of ordinary skill in the art would understand that combining the teachings of Kaur et al. with van Breemen et al. cannot render the claimed method obvious.

Applicants have identified the specific teachings in van Breemen et al. that elucidate a proper interpretation of the journal article to assist in examination of the application.

Journal Article Disclosure	Journal Article Citation
Ligand-receptor ***complexes*** were purified by ***ultrafiltration*** and	First paragraph of page 2159 at approximately line 10 in column 1

then ***dissociated*** using methanol to elute the ligands	with emphasis added
Based on an extension of our method for pulse ***ultrafiltration*** measurement of affinity constants for ligand-receptor ***bonding***	Second paragraph of page 2159 at approximately line 8 in column 2 with emphasis added
A preliminary report on the use of pulsed ***ultrafiltration*** mass spectrometry for the measurement of classical equilibrium ***binding*** constants	Second paragraph of page 2160 at approximately line 18 in column 1 with emphasis added
The mobile phase was changed to methanol-water to ***dissociate*** the enzyme-ligand ***complex*** and thereby release the bound ligands for identification by electrospray mass spectroscopy	Fifth paragraph of page 2160 at approximately line 40 in column 2 with emphasis added
Bound ligands were eluted into the mass spectrometer	Sixth paragraph of page 2160 at approximately line 52 in column 2 with emphasis added
Bound EHNA was released into the mass spectrometer by eluting the [ultrafiltration] chamber using methanol in water	First paragraph of page 2161 at approximately line 10 in column 1 with emphasis added
During pulsed ultrafiltration, ligand-receptor ***complexes*** remain in solution in the chamber while unbound compound are washed away	Second paragraph of page 2161 at approximately line 30 in column 1 with emphasis added
The ligand-receptor ***complex*** is	Second paragraph of page 2161 at

disrupted so that the ligands are released to the mass spectrometer	approximately line 36 in column 1 with emphasis added
After infusion of a dilution solution of the compounds through a ultrafiltration chamber ***bound*** ligands were released into the mass spectrometer	First paragraph of page 2162 at approximately line 3 in column 1 with emphasis added
Methanol was introduced into the mobile phase to ***dissociate*** the enzyme-ligand ***complex*** and release bound ligands for ***identification*** by electrospray mass spectrometry	Second paragraph of page 2162 at approximately line 15 in column 1 with emphasis added

The teachings clearly evidence that van Breemen et al. discloses ultrafiltration methods that are used to ***exclude*** ligand-receptor ***complexes*** from unbound material. The journal article does not suggest performing an ultrafiltration or exclusion of a ***complex*** that has been ***dissociated*** into a receptor and an ***unbound*** ligand as required by the claimed method.

An individual of ordinary skill in the art would only be motivated to substitute the ***first*** size exclusion medium disclosed by Kaur et al. with the ***ultrafiltration*** method taught by van Breemen et al. This substitution is practical as the ***first*** size exclusion medium described in Kaur et al. is specifically used to ***exclude*** ligand-receptor ***complexes*** from unbound material just as the ultrafiltration disclosure of van Breemen et al. A motivation is not present that would suggest to an individual within the art to use the ultrafiltration method of van Breemen et al. to ***separate*** a ***dissociated*** mixture comprising a receptor and an

unbound ligand as the journal article is entirely unrelated to excluding molecules from a ***dissociated*** receptor and ***unbound*** ligand mixture prior to analysis via a mass spectrometry or related method.

The patent laws require that each limitation of the claims under consideration be disclosed in a reference(s) in order to establish a prima facie basis for obviousness. Applicants have demonstrated that a combination of the cited journal articles does not describe using a ***second*** size exclusion medium to exclude a ***complex*** that has been ***dissociated*** into a receptor and an ***unbound*** ligand as required by the claimed method. The journal articles plainly do not disclose a limitation regarding a ***second*** size medium. The articles also do not teach each of the limitations of the method as arranged in the pending claims. The pending claims particularly require ***dissociation*** of the protein-target binding ligand complex ***prior*** to subjecting the dissociated mixture to a ***second*** size exclusion medium. The arrangement of limitations recited in the claimed method are provided to perform the invention. The journal articles cited by the Examiner are not capable of performing the invention as arranged in the claims.

The patent laws have also settled that a reference(s) cannot be interpreted in a manner that would obviate the advantages that it discloses or teaches. Applicants contend that the Examiner has not fully considered the advantages of pulsed ultrafiltration-mass spectrometry as suggested by van Breemen et al. The journal article to van Breemen et al. distinctly characterizes the advantages of performing ultrafiltration of ligand-receptor ***complexes*** then ***dissociating*** the excluded complexes ***prior*** to analysis via a mass spectrometer. These advantages also

underscore the experimental concepts presented by van Breemen et al. The Examiner has avoided the plain teachings of these advantages in applying van Breemen et al. to render the claimed method obvious.

In summary, the claimed method requires a ***second*** size exclusion medium to exclude a ***complex*** that has been ***dissociated*** into a receptor and an ***unbound*** ligand. The journals articles to Kaur et al. and van Breemen et al. each disclose subjecting a ligand-receptor ***complex*** to a size exclusion medium to exclude unbound material and then ***dissociating*** the complexes ***prior*** to analysis via a mass spectrometer. The articles do not suggest or mention using a ***second*** size exclusion medium that would ***exclude*** molecules that are present in the ***dissociated*** receptor and ***unbound*** ligand mixture prior to an analysis via a mass spectrometer or related method. Thus, Applicants submit that the rejections by the Examiner have been overcome as claims 1-14, 21 and 22 are not obvious based on Kaur et al. in view of van Breemen et al.

New Claim Rejections 35 U.S.C. § 102

The Examiner has rejected claims 1-5, 13, 14, 21 and 22 as anticipated by International Publication No. WO 97/01755 to Jindal et al. The Examiner has asserted that Jindal et al. teach each of the limitations of the claimed method. Applicants respectfully submit that Jindal et al. do not disclose passing a reaction mixture or ***complex*** through a ***first*** size exclusion medium and subjecting the size excluded reaction mixture to ***dissociation*** prior to passing the dissociated mixture through a ***second*** size exclusion medium as required by claim 1. The reference merely

teaches a method for screening a sample to select a ligand to a target of interest.

The target-ligand ***complex*** taught by Jindal et al. might also be separated from unbound components using a first and ***second*** size exclusion means. The reference, however, clearly does not disclose ***dissociation*** of a complex prior to passing the dissociated mixture through a ***second*** size exclusion medium. The Examiner has suggested that the mention of "complex dissociates" by Jindal et al. anticipates subjecting the size-excluded reaction mixture of claim 1 to conditions promoting ***dissociation*** of the complex ***prior*** to subjecting the dissociated mixture to a ***second*** size exclusion medium. Applicants underscore that the teaching of complex dissociates by Jindal et al. was ***only*** in regard to the selection of a peptide library.

The peptide library taught by Jindal et al. is not involved in any sort of method that would anticipate claim 1. Specifically, the passing reference to selecting a peptide library as a theoretical basis for screening does not anticipate a method in which a ***dissociated*** protein target and ***unbound*** ligand are subjected to a ***second*** size exclusion medium. Jindal et al. is completely silent with regard to ***dissociation*** of a complex prior to passing the dissociated mixture through a ***second*** size exclusion medium as required by claim 1. The patent laws, however, require that an individual reference disclose each limitation of the claims under consideration for anticipation. Thus, Applicants submit that Jindal et al. do not anticipate the claimed method.

New Claim Rejections 35 U.S.C. § 103

The Examiner has rejected claims 1-14 21 and 22 as obvious based on International Publication No. WO 97/01755 to Jindal et

al. in view of several other references. The Examiner has asserted that the references in combination teach each of the limitations of the claimed method. Applicants respectfully submit, however, that Jindal et al. do not disclose passing a reaction mixture or ***complex*** through a ***first*** size exclusion medium and subjecting the size excluded reaction mixture to ***dissociation*** prior to passing the dissociated mixture through a ***second*** size exclusion medium as required by claim 1. The reference merely teaches a method for screening a sample to select a ligand to a target of interest.

The target-ligand ***complex*** taught by Jindal et al. might also be separated from unbound components using a first and ***second*** size exclusion means. The reference does not disclose ***dissociation*** of a complex prior to passing the dissociated mixture through a ***second*** size exclusion medium. The Examiner has suggested that the mention of "complex dissociates" by Jindal et al. renders obvious subjecting the size-excluded reaction mixture of claim 1 to conditions promoting ***dissociation*** of the complex ***prior*** to subjecting the dissociated mixture to a ***second*** size exclusion medium. Applicants underscore that the teaching of complex dissociates by Jindal et al. was ***only*** in regard to the selection of a peptide library.

The peptide library taught by Jindal et al. is not involved in any sort of method that would render claim 1 obvious. Specifically, the passing reference to selecting a peptide library as a theoretical basis for screening does not render obvious a method in which a ***dissociated*** protein target and ***unbound*** ligand are subjected to a ***second*** size exclusion medium. Jindal et al. is completely silent with regard to ***dissociation*** of a complex prior to passing the dissociated mixture through a ***second*** size exclusion medium as required by claim 1. The other references cited by the Examiner

also wholly fail to overcome the deficiencies of Jindal et al. Thus, Applicants submit that Jindal et al. do not render the claimed method obvious.

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CONCLUSION

Based on the remarks presented herein, reconsideration and withdrawal of the rejections by the Examiner and allowance of the application with the pending claims are respectfully requested.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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